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6-*O*-Picolinyl and 6-*O*-Picoloyl Building Blocks As Glycosyl Donors with Switchable Stereoselectivity

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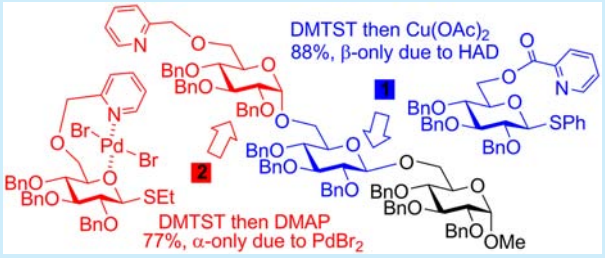
Supporting Information

ABSTRACT: Remote 6-*O*-picolinyl or 6-*O*-picoloyl substituents often provide high β-selectivity due to H-bond-mediated aglycone delivery (HAD). Herein it has been demonstrated that if the nitrogen atom of the 6-*O*-picolinyl or picoloyl moiety is temporarily blocked by coordination to a metal center (Pd), it cannot engage in HAD-mediated β-glycosylation. Hence, the stereoselectivity of 6-*O*-picolinyl/picoloyl-assisted glycosylations can be "switched" to α-selectivity.



The aim of stereocontrolling chemical glycosylation reactions has persistently captured the attention of the glycoscience community.[1,2] Many methods have been developed, and a number of techniques for the stereocontrolled synthesis of 1,2-*cis*[3] and 1,2-*trans*[4] glycosides are now available. The use of a single glycosyl donor to obtain either 1,2-*cis* or 1,2-*trans* glycosides by changing the reaction temperature, solvent, or reagents has also been reported.[5−7] However, examples wherein the switchable stereoselectivity can be achieved with high utility, reproducibility, and two-way stereoselectivity are still rare.

The main goal of the study presented herein is the development of a novel method for stereocontrolled glycosylation based on glycosyl donors with switchable stereoselectivity. Previously, our group introduced a series of glycosyl donors with pyridine-based protecting groups, picolinyl (Pic)[8−10] or picoloyl (Pico).[10−13] When placed at the remote C-6 position, these directing groups provided high β-selectivity due to the H-bond-mediated aglycone delivery (HAD, **A**, Figure 1).[10,14] We conceptualized that if the nitrogen atom of the Pic or Pico moiety were temporarily blocked by coordination to the metal center, it would not engage in HAD during glycosylation with the consequence that the stereoselectivity might be "switched" (**B**). The

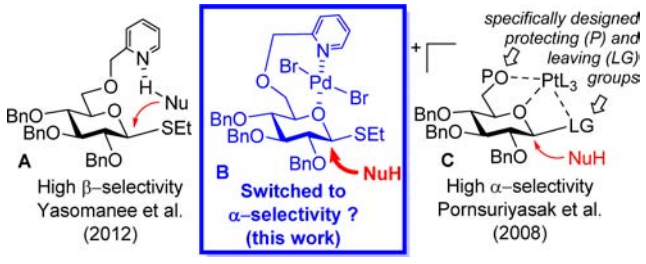
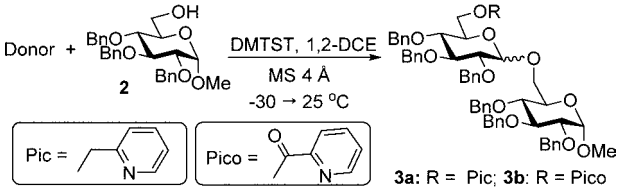
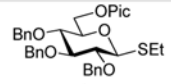
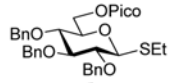
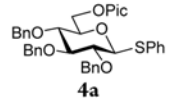
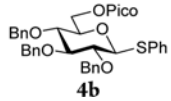


Figure 1. Concept of switchable stereoselectivity.

Table 1. High β-Selectivity Achieved with HAD



entry	donor	time, h	product (yield/%, α/β ratio)
1	 **1a**	5	**3a** (93, 1/2.4)
2	 **1b**	1.5	**3b** (96, β only)
3	 **4a**	8	**3a** (79, 1/1.5)
4	 **4b**	8	**3b** (88, β only)

anticipated significance of this approach would be the use of a single glycosyl donor for the synthesis of either a 1,2-*cis* or 1,2-*trans* linkage on demand, a trait that is rather uncommon in glycosylation.[15]

It should be noted that the role of metal complexation in chemical glycosylation remains practically unexplored because common oxygen-containing carbohydrates typically form

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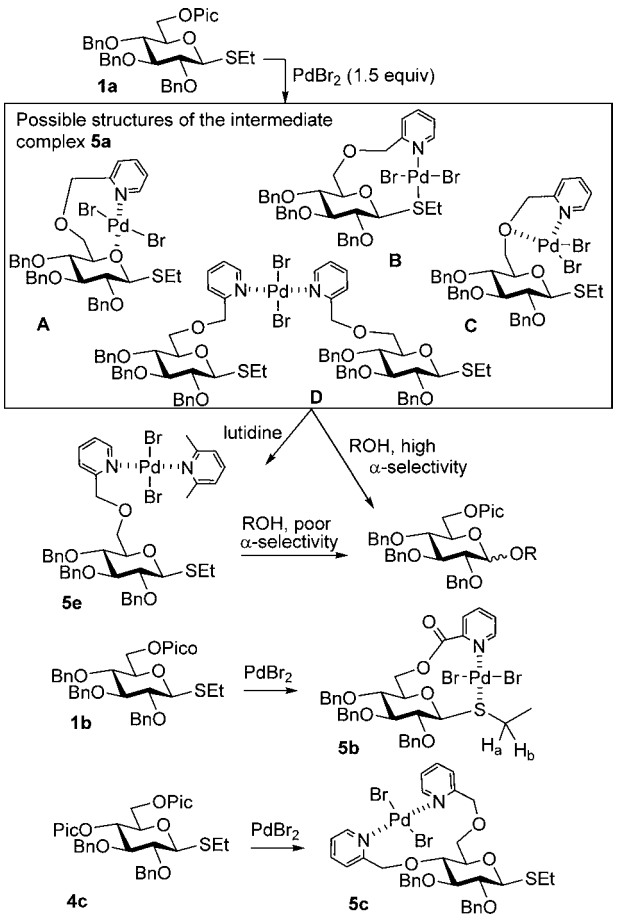
Scheme 1. Anticipated Pathways for Enhancing α-Stereoselectivity with Complexed 6-*O*-Picolinyl Donors



unstable flexidentate complexes.[16,17] Our previous study showed that targeted coordination can be achieved by the introduction of *N*-Lewis base substituents. Thus, we demonstrated that multidentate metal coordination to the leaving group along with O-5, and/or a protecting group at O-6, has a strong effect on the stereoselectivity of chemical glycosylation (**C**, Figure 1). Specifically, we designed pyridine-based protecting groups for O-6 in that study.[18] We hypothesized that combining the conventions of these two latter approaches would give us a convenient tool for achieving switchable stereoselectivity with use of the same glycosyl donor, with noncomplexed (**A**) leading to β-selectivity and complexed (**B**, Figure 1) leading to α-selectivity. Among the possibilities, the picolinyl group offers a suitable platform for providing nitrogen atoms that form stable metal complexes. The high stability of such complexes during the glycosylation process would be key for providing the desired effects that might lead to enhanced stereocontrol.

Previously we reported that a coupling of *S*-ethyl donor **1a**[10] with glycosyl acceptor **2**[19] in the presence of dimethyl(thiomethyl)sulfonium triflate (DMTST)[20] provided disaccharide **3a** in 93% yield (α/β = 1/2.4, entry 1, Table 1).[10] The β-stereoselectivity could typically be further improved by performing essentially the same reaction at high dilution (5 mM concentration of the donor).[10] The use of picoloylated donor **1b**[10] (β-only, entry 2) often gave a further enhancement of the β-stereoselectivity.[10] Analogous *S*-phenyl glycosyl donors **4a** and **4b**, prepared specifically for this study (see the Supporting Information for the synthesis), provided similar results surveyed in entries 3 and 4.

We then turned our attention to investigation of glycosylations in the presence of $PdBr_2$. For this, we developed a convenient three-step one-pot protocol involving sequential complexation, glycosylation, and decomplexation. Accordingly, donor **1a** (1.3 equiv with respect to the acceptor) was treated with $PdBr_2$ (1.5 equiv with respect to the donor) in the presence of glycosyl acceptor **2** and molecular sieves (4 Å) in CH_2Cl_2 for 3 h at rt. During this time, donor **1a** was completely converted into its Pd-complex (**5a**). After that, the reaction mixture was cooled to −30 °C, DMTST (2.0 equiv. with respect to the donor) was added, and the resulting mixture was allowed to warm to rt and stirred for 6−8 h. At this stage, disaccharide **3a** was still present as its $PdBr_2$ complex. DMAP was added to conduct the decomplexation, which was typically completed in 30 min. As a result, disaccharide **3a** was isolated in 97% yield with some α-selectivity (α/β = 2.1/1, entry 1, Table 2). Applying essentially the same reaction conditions to glycosylation of acceptors **6**, **8**, and **10**,[21,22] we obtained the corresponding disaccharides **7**, **9**, and **11** in excellent yields of 85−96% and preferential α-selectivity (α/β = 4.5−13.6/1, entries 2−4). Glycosylation of glycosyl acceptor **2** with *S*-phenyl donors **4a** or **4b** provided a similar outcome in terms of both yields and stereoselectivities (entries 5 and 6).

In a commitment to further enhance α-stereoselectivity, we screened various reaction conditions. While we have practically seen no effect of the reaction temperature, we determined that a reduced amount of DMTST (1.3 equiv. with respect to the donor) helps improve stereoselectivity. This effect was particularly strong in the case of glycosyl donor **4a**, which provided disaccharide **3a** with excellent α-selectivity and in high yield (α/β = 12.5/1, 89%, entry 7). The enhancement of stereoselectivity obtained with donor **4b** was not so pronounced, but still noticeable (α/β = 6.3/1, 88%, entry 8). Encouraged by these results, we glycosylated a range of the secondary acceptors **6**, **8**, and **10** and obtained excellent results for the synthesis of the respective disaccharides **7**, **9**, and **11** (entries 9−11). A particularly impressive result for the synthesis of the 1 → 6-linkage was obtained with benzoylated acceptor **12**[23] wherein the formation of disaccharide **13** was accomplished in high yield and with complete α-selectivity (entry 12). For comparison, we also synthesized and tested 4,6-di-*O*-picolylated donor **4c**. The three-step one-pot procedure was practically ineffective in this case, and the selectivity was poor (entry 13).

Having achieved good levels of stereocontrol we were curious to look into the structure of possible reaction intermediates. As mentioned, upon treatment of **1a** with $PdBr_2$, complex **5a** forms entirely, but its ligation mode remained uncertain. The NMR analysis of **5a** showed the presence of two distinct structures in the ratio of 4/1. Interestingly, *S,N*-complex **B** (Scheme 1) is not formed herein, as evident from the lack of splitting of the SCH_2 protons that would have occurred otherwise,[24] similarly to that observed for the formation of complex **5b** from 6-*O*-picoloylated donor **1b** (see the Supporting Information for details).

Although previously we detected the formation of bis-ligand dimeric complexes,[25] we believe that *N,N*-complex **D** is not forming here for the reason outlined below. Hence, it is possible that **5a** represents an interchangeable mixture of *N,O*-

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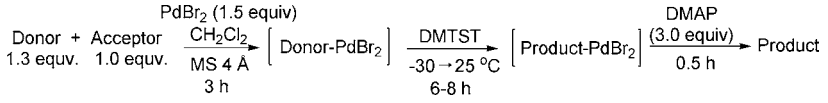
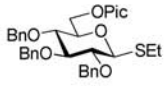
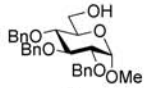
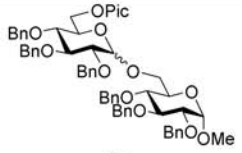
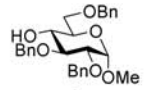
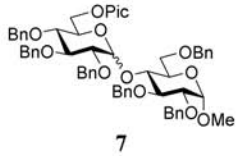
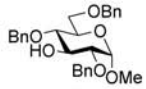
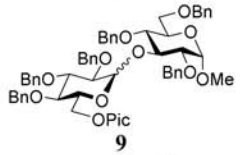
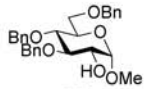
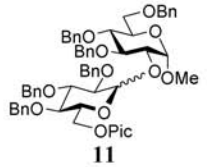
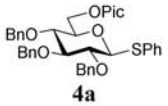
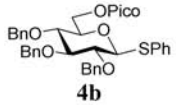
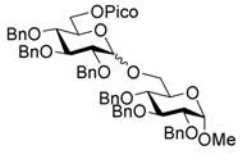
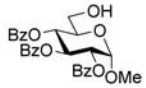
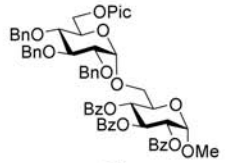
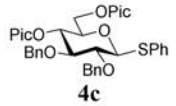
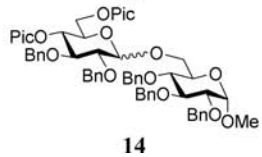
Table 2. High α-Stereoselectivity Can Be Achieved with $PdBr_2$-Complexed 6-*O*-Pic/Pico Glycosyl Donors



entry	donor	acceptor	DMTST, equiv	product	yield/%, α/β ratio
1	 **1a**	 **2**	2.6	 **3a**	97, 2.1/1
2	**1a**	 **6**	2.6	 **7**	96, 8.3/1
3	**1a**	 **8**	2.6	 **9**	94, 4.5/1
4	**1a**	 **10**	2.6	 **11**	85, 13.6/1
5	 **4a**	**2**	2.6	**3a**	97, 2.5/1
6	 **4b**	**2**	2.6	 **3b**	84, 3.9/1
7	**4a**	**2**	1.7	**3a**	89, 12.5/1
8	**4b**	**2**	1.7	**3b**	88, 6.3/1
9	**4a**	**6**	1.7	**7**	69, 8.1/1
10	**4a**	**8**	1.7	**9**	94, 6.7/1
11	**4a**	**10**	1.7	**11**	84, 22.5/1
12	**4a**	 **12**	1.7	 **13**	89, α-only
13	 **4c**	**2**	1.7	 **14**	73, 1/1.4

complexes **A** and **C**, typical for unstable oxygen-containing flexidentate complexes of carbohydrates with palladium(II).[16,17] The treatment of complex **5a** with lutidine led to the formation of a relatively stable complex **5e**, the structure of which was confirmed by spectral techniques. For comparison, complex **5c** formed from dipicolylated donor **4c** did not undergo the ligand exchange with lutidine and required a stronger base (DMAP) to decomplex. In our opinion, if **5a** existed as bis-ligand structure **D**, it would also be expected to remain stable in the presence of lutidine. Similarly to that of other *N,N*-ligated intermediates, complex **5e** provided very poor stereoselectivity in glycosylation. A

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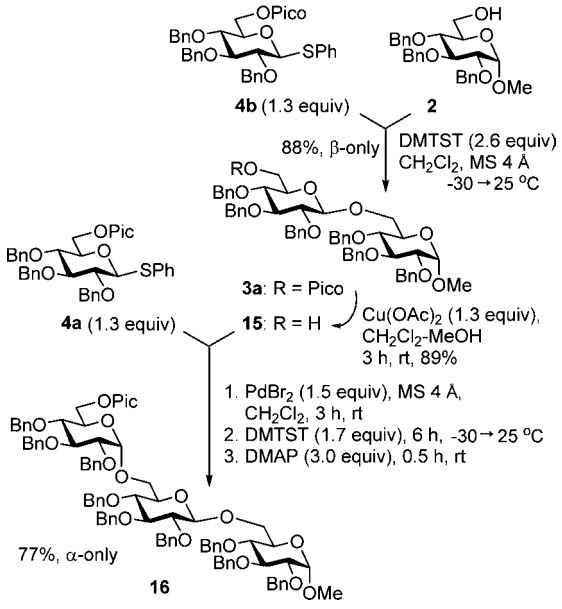
Scheme 2. Synthesis of *cis*–*trans*-Patterned Trisaccharide 16



similar structure determination experiment with *S*-phenyl donor **4a** led to the formation of the respective complex **5d** (see the Supporting Information), which exists as a 2/1 mixture as evident from its NMR.

To demonstrate the utility of the newly developed approach in the context of multistep oligosaccharide synthesis we performed the synthesis of *cis*–*trans*-patterned trisaccharide **16** (Scheme 2). HAD glycosylation of acceptor **2** with donor **4b** gave disaccharide **3a**. The picoloyl group of the latter was selectively removed with copper(II) acetate, and the resulting acceptor **15** was reacted with donor **4a** in the presence of $PdBr_2$ and DMTST to afford trisaccharide **16** with complete stereoselectivity in both steps.

In conclusion, we have shown that if the nitrogen atom of the 6-*O*-picolinyl or picoloyl moiety is temporarily blocked by coordination to a metal center (Pd), it cannot engage in HAD-mediated β-glycosylation, and hence the stereoselectivity of 6-*O*-Pic/Pico-assisted glycosylations can be "switched" to α-selectivity. The utility of this technique was demonstrated by the synthesis of a *cis*–*trans* linked trisaccharide via sequential *trans*–*cis* glycosylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02110.

Additional experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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